Responses to Comments Submitted by the Formaldehyde Epidemiology Toxicology and Environmental Group (FETEG), Inc.

Comment 1: Potential cancer risk. OEHHA incorrectly concludes that the 1980 bioassay by the Chemical Industry Institute of Toxicology (CIIT) is the "most quantitatively useful evidence for the carcinogenicity of formaldehyde."[1] A great deal of evidence regarding formaldehyde's potential carcinogenicity, and its mode of action in particular, has been developed in the 20 years since that seminal bioassay; indeed, most of this follow-up work was done by scientists at CIIT. In 1999 a team of researchers at CIIT, with input from U.S. EPA, Health Canada, and peer reviewers, published a thorough evaluation of potential cancer risk from formaldehyde, incorporating over twenty years of research and integrating various toxicological, mechanistic, and dosimetric data.[2] This CIIT risk assessment presents new estimates for the risk of developing cancer from formaldehyde exposure, and incorporates vastly more data into the biologically based model than ever used by the U.S. EPA in 1987 with a linear default calculation. FETEG strongly urges OEHHA to consider the data provided in this more recent CIIT report in making any risk management decisions concerning formaldehyde.

The CIIT 1999 biologically-based CIIT model relies on detailed information on doses delivered to each area of the respiratory tract in rats and humans. The model is based on an assumption of genotoxicity at low doses, so it still retains a linear shape at low doses. At higher doses, however, the model is driven by cytotoxicity and cell proliferation as the mode of action for carcinogenesis, producing a non-linear dose-response curve at the upper end of the dose range. The model's risk estimates have been validated against epidemiological data on formaldehyde workers.

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[1] OEHHA, Public Review Draft for Formaldehyde, at 15 (Mar. 2001) (hereafter "Public Review Draft").

[2] Chemical Industry Institute of Technology, *Formaldehyde: Hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation* (revised ed. 1999) (hereafter "CIIT Report") (copy attached as Exhibit A). Executive summary available at www.ciit.org. Several manuscripts describing the results of this study are in press or in preparation.

- CIIT evaluated two exposure scenarios using this model. The resulting cancer risk estimates are many orders of magnitude lower than the 1987 and 1991 U.S. EPA estimates, even though the CIIT estimation still includes many conservative assumptions. lifetime. Under these conditions, the model predicts the increased lifetime risk of cancer is 1.0×10^{-7} or 1 in 10,000,000 (ten million) for smokers and 4.1×10^{-9} or 4.1 in 1,000,000,000 (one billion) for non-smokers.

Thus, at doses below the inflection point of the dose-response curve (driven by cytotoxicity), predicted human cancer risk is negligible.

The new clonal growth model is still conservative in that it tends to overpredict risk, according to CIIT. However, by using a data-rich and parameter-rich model, the new assessment greatly reduces the uncertainty levels associated with formaldehyde cancer risk estimates. Health Canada has cited this CIIT risk assessment in its Draft Assessment Report for Formaldehyde under the Priority Substances List Program.[3] We understand the U.S. EPA plans to incorporate the CIIT cancer risk assessment into IRIS and will submit the IRIS package for Science Advisory Board Review this year.[4]

Thus, OEHHA should use this recently completed CIIT biologically-based model because it represents the best available science for evaluating formaldehyde's cancer risk. Reliance on the 1987 IRIS value is inappropriate.

RESPONSE 1: The purpose of the draft document is to prioritize TACs to develop a list of those TACs that "may cause infants and children to be especially susceptible to illness" as required in Health and Safety Code Section 39665.1. It is not to revisit the unit risk factor for formaldehyde. Our unit risk factor went through public review and peer review by the state's Scientific Review Panel on Toxic Air Contaminants. Secondly, OEHHA did not, as the comment assumes, rely on U.S. EPA's value in IRIS.

[3] This document is available at http://www.ec.gc.ca/cceb1/eng/public/formaldehyde_e.html.

[4] For further information, contact Annie M. Jarabek at EPA (by phone at 919-541-4847, or by e-mail at jarabek.annie@epa.gov).

We developed our own value which incorporated the effects of cell proliferation and DNA-protein crosslinks into the calculations of the cancer potency. Third, the CIIT report has not undergone public review of review by the EPA's Science Advisory Board, so it is not an official USEPA risk assessment. Fourth, the placement of formaldehyde into Tier 1 is not solely based on its carcinogenicity, although that plays a role in prioritization of formaldehyde as an important TAC.

OEHHA acknowledges the useful work at CIIT over the decade since our TAC document for formaldehyde was adopted, and has cited in our draft document the major portions of the work that is published. In response to the comment we propose to strike the word "most" from the phrase "most quantitatively useful" in describing the early CIIT work.

COMMENT 2: Epidemiological studies. The Public Review Draft contains a very limited discussion of epidemiological studies to support a link between formaldehyde and elevated risks of nasal and lung cancer. As part of the 1999 CIIT report (discussed above), researchers conducted a comprehensive review of available epidemiology studies. This review contains several more current studies than those cited in the OEHHA document.

With respect to nasal and nasopharyngeal cancers, CIIT found that "excesses of cancers of the nasal or nasopharyngeal cavities have not been observed consistently in cohort studies. Where there have been excesses, there has been little evidence of exposure-response; however, the total number of observed tumors in these investigations was small."[5] It was also noted that there "is little convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers occupationally exposed to formaldehyde."[6] In fact, the recent evaluation of formaldehyde by IARC considered the relationship between formaldehyde and nasal

[5] CIIT Report, at 4-9.

[6] *Id.*

cancer to be limited, finding that the association observed in some studies resulted from bias, chance, or confounding with other studies. [7]

As for lung cancer, CIIT found "there is little evidence for a causal relationship between exposure to formaldehyde and lung cancer in case control and cohort studies conducted to date. Increases in mortality or incidence have not been observed consistently, and where examined, there has been consistently no evidence of an exposure-response relationship."[8] OEHHA relies heavily on the 1986 Blair *et al.*[9] study to support its conclusion about elevated rates of lung cancer. In that study, researchers observed a slight but statistically significant (1.3 fold) excess of deaths due to lung cancer among the subcohort of white male industrial workers with greater than 20 years since first exposure to formaldehyde. However, "results of a number of follow-up studies within this industrial group have provided little additional evidence of exposure-response (i.e., cumulative, average, peak, duration, intensity) except in the presence of other substances."[10] Thus, OEHHA's use of this study should be more carefully limited.

As noted previously in this section, several recent reviews of the epidemiological data have been published, but not cited in the Public Review Draft. IARC classified formaldehyde in Category 2A, finding the epidemiology "limited." Collins *et al.* conducted an updated meta-analysis of formaldehyde exposure and upper respiratory tract cancers and concluded that available studies do not support a causal relation between formaldehyde exposure and human nasopharyngeal cancer.[11] Another review by former NCI researcher Joseph McLaughlin concluded: "When the epidemiologic data on formaldehyde and human cancer are examined in light of the widely accepted causal

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[7] World Health Organization, International Agency for Research of Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans, 62:217 (1995).

[8] *Id.* at 4-10.

[9] A. Blair *et al.*, *Mortality Among Industrial Workers Exposed to Formaldehyde*, 76 JNCI 1071-84 (1986).

[10] CIIT Report, at 4-11.

[11] Journal of Occupational and Environmental Medicine 39: 639-50 (1997).

criteria of strength of the association, consistency and specificity of results, dose-response effects, and biologic coherence and plausibility, the studies published so far fail to provide credible causal evidence."[12] In ECETOC Technical Report No. 65 Formaldehyde and Human Cancer Risk (1995), the Task Force concludes: "After a careful review of the cytologic, cytogenic, and epidemiological studies there is an absence of evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk." OEHHA should factor the conclusions from these studies into its prioritization determination for formaldehyde.

RESPONSE 2: The commenter apparently disagrees that formaldehyde should be considered a carcinogen in humans. As noted in the comment, IARC has classified formaldehdye as 2A, based on limited evidence in humans. There are a number of studies in the epidemiological literature supporting a link between formaldehyde and elevated risks of cancers of the upper respiratory tract. Stayner (1988) reports a relative risk of 3.4 (90% CI = 1.2-7.9) for buccal cancer. Blair *et al* (1986) reports elevated risks for nasopharyngeal cancer (RR = 3.0; 90%CI = 1.3-5.9). Liebling *et al* report a relative risk of 8.70 (90%CI = 1.50-27.33) for buccal cancer. Formaldehyde is clearly carcinogenic in rodent bioassays (Swenberg *et al.*, 1980 a,b; Kerns *et al.*, 1983 and others), and is genotoxic. During the open public process that California has for identifying TACs, the data on formaldehyde carcinogenicity up to that time point was fully evaluated. IARC has not changed their classification based on Collins *et al* as cited in the comment. Consequently, our understanding of the scientific evidence continues to indicate that Cal/EPA should consider formaldehyde as a potential human carcinogen..

[12] McLaughlin, *Formaldehyde and cancer: a critical review*, Int. Arch. Occup. Environ. Health (1994).

COMMENT 3: Genotoxicity. As noted in the CIIT review, the results of genotoxicity studies in human population "are somewhat equivocal as noted in the IARC review (1995)."[13] Human studies showed that "at best, a very weak positive response is indicated, usually in nontarget cells for tumor formation."[14] In *in vivo* studies involving the exposure of laboratory animals to formaldehyde, CIIT described formaldehyde as "being weakly mutagenic in some assays and not detectable as mutagenic in others," and as "weakly" mutagenic in *in vitro* studies.[15] Thus, "[a]lthough formaldehyde exhibits weak genotoxic activity, whether this contributes to an increased risk at low exposure levels is not clear."[16]

OEHHA should clarify in the Public Review Draft the relationship between DNA-protein crosslinks (DPX) and carcinogenesis. Formaldehyde-induced carcinogenesis is dependent upon cytotoxicity. Increased cellular proliferation generally results as a consequence of toxicity to epithelial cells. Regenerative cell proliferation increases the number of DNA replications. This increases the probability of DNA replication error, resulting in a mutation. The CIIT Report concludes that formaldehyde is carcinogenic only at concentrations that induce the proliferative regenerative response associated with cytotoxicity.[17]

Because the respective roles of DPX, mutation, and cellular proliferation in carcinogenesis are not completely clear, in its 1999 study, CIIT "attempted to identify the alternative that would lead to a prediction of higher risk in the final model."[18] Under this principle, CIIT built into its model data regarding the potential genotoxicity of formaldehyde. Inclusion of this component achieved the most conservative results for

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[13] *Id.* at xxi.

[14] *Id.* at xxii, 4-28.

[15] *Id.* at xxii, 4-29, -30.

[16] *Id.* at 5-3 (emphasis added).

[17] *Id.* at xxv.

[18] *Id.* at 8-11.

quantitative risk assessment, but is not meant to support a finding that formaldehyde is genotoxic.

"Formaldehyde induces DPX in nasal mucosal cellular DNA of rats with a concentration response that is highly non-linear."[19] More specifically:

The concentration-response curve for formaldehyde-induced cytotoxicity and regenerative proliferation is highly nonlinear. This nonlinearity is a consequence of the fact that saturable protective mechanisms (e.g., mucous layer, oxidative metabolism) reduce the amount of formaldehyde reaching the squamous epithelium at low exposure concentrations. Not until these protective mechanisms are overwhelmed will a cytotoxic (or carcinogenic) effect be observed. The two factors that therefore appear to be necessary, but not sufficient, for tumor formation following formaldehyde exposure, namely DPX and regenerative cell proliferation, both have highly nonlinear responses as a function of concentration or of flux of formaldehyde into tissue.[20]

For purposes of modeling, however, "[f]ormaldehyde is assumed to act as a direct mutagen," with its intensity described as being proportional to DPX.[21] However, "[a]lthough formaldehyde exhibits weak genotoxic activity, whether this contributes to an increased risk at low exposure levels is not clear."[22]

RESPONSE 3: The comment indicates that the genotoxic activity of formaldehyde is deemed "weak" by CIIT. OEHHA reviewed the evidence on genotoxicity in its analysis of formaldehyde during the TAC identification process, and concluded that formaldehyde was genotoxic and a potential human carcinogen. The regulatory process has identified formaldehyde as a toxic air contaminant primarily based on carcinogenicity. We still stand by those decisions. However, this document's purpose is to examine potential for health impacts to infants and children. The basis for our consideration of formaldehyde

[19] *Id.* at xxv.

[20] *Id.*

[21] *Id.* at xxxiii.

[22] *Id.* at 5-3.

as a TAC that may cause infants and children to be especially susceptible to illness is primarily the respiratory effects and less so the carcinogenicity or genotoxicity of formaldehyde.

COMMENT 4: Non-cancer effects. The studies OEHHA cites with respect to asthma, pulmonary function, and immunotoxicity are not representative of the weight of evidence. For a more current and thorough evaluation of the scientific literature concerning non-cancer endpoints, such as irritation, pulmonary function, and asthma, FETEG urges OEHHA to review the attached papers by Joel Bender[23] and Dennis Paustenbach *et al.*[24] Dr. Bender reviewed the human data on irritation and respiratory effects. The Paustenbach paper represents the results of deliberations of a panel of experts convened to review approximately 150 published articles to determine an appropriate occupational exposure level for formaldehyde. Both these papers criticize several of the studies relied upon by OEHHA to support its conclusions about asthma and pulmonary function effects, and discuss additional studies that should be included in OEHHA's review.

RESPONSE 4: We disagree that the citations, which we have provided with respect to asthma, etc., are not representative of the weight of the evidence. OEHHA evaluated the paper by Paustenbach in our review of the literature during the evaluation of formaldehyde for the derivation of chronic and acute Reference Exposure Levels. While the paper has some value for evaluating occupational exposure levels, we found it of limited utility in evaluating community exposure levels which are intended to protect the general public including infants and children, the ill, elderly, and other sensitive subpopulations. In addition, the papers we cited regarding evaluation of children's

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[23] J. Bender, *The Use of Non-Cancer Endpoints as a Basis for Establishing a Reference Concentration for Formaldehyde* (2000) (attached as Exhibit B) (manuscript submitted for publication to the Journal of Regulatory Toxicology and Pharmacology).

[24] D.Y. Paustenbach *et al.*, A Recommended Occupational Exposure Limit for Formaldehyde Based on Irritation, 50 J. Toxicology and Environ. Health 217-63 (1997) (attached as Exhibit C).

respiratory effects are not cited in the paper by Paustenbach *et al* because they do not describe occupational exposures which is what Paustenbach *et al* ultimately address. The paper by Bender is an as yet unpublished report where the author concludes that the existing studies are inadequate to identify a NOEL for acute sensory irritation. Our chronic REL is based on upper and lower airway irritation and eye irritation in humans and inflammatory and hyperplastic changes in the nasal mucosa of humans and animals. Thus, the relevance to our chronic REL of the Bender report is limited. In addition, we do not agree with all of Bender's conclusions regarding sensory irritation from formaldehyde. Both the acute and chronic REL reports underwent public review and review by the State's Scientific Review Panel on Toxic Air Contaminants. The RELs were endorsed by the SRP with recognition of the uncertainties in the studies used to generate the REL. The chronic REL is a factor in the placement of formaldehyde into Tier 1 because measurements of formaldehyde in urban ambient air in California approach the chronic REL and can be higher in urban areas and indoors.

COMMENT 5: Formaldehyde exposure has not been shown to cause asthma. By way of example, Dr. Frigas and others at the Mayo Clinic conducted bronchial challenge tests with formaldehyde in 13 patients suspected of having formaldehyde-induced asthma. The authors concluded: "[T]esting with a formaldehyde bronchial challenge did not provoke asthma in 13 selected patients with symptoms suggestive of asthma and a history of exposure to formaldehyde gas. Cases of formaldehyde-induced asthma may be rare."[25] Grammar *et al.* concluded that immunologically-mediated asthma caused by formaldehyde is extremely rare, if it exists at all. Witek *et al.* concluded that in mild asthmatics, short term (40 minute) exposure to 2 ppm does not induce acute airway obstruction. In a study by Pross *et al.*, no effect on the immune response was observed in

[25] Frigas, *et al.*, Bronchial Challenge with Formaldehyde Gas Complete, Mayo Clinic Proceedings, vol. 59, 295-299 (May 1984).

asthmatic subjects exposed to formaldehyde at 1 ppm.[26] Paustenbach *et al.* cite a number of studies leading them to conclude asthmatics are no more sensitive to formaldehyde than healthy individuals, including studies by Sheppard,[27] Sauder,[28] Kulle,[29] and Green.[30]

FETEG urges OEHHA to consider the attached papers and the studies cited in them before finalizing the Public Review Document for Formaldehyde. OEHHA should also consider the discussion below concerning the Krzyzanowski *et al.* study on pulmonary function effects in children exposed to formaldehyde.

RESPONSE 5: OEHHA agrees that the data on exacerbation of asthma by formaldehyde are mixed with some studies indicating asthma can be exacerbated and others indicating the opposite. As detailed in the report, the effects on asthmatics appear to be dependent on prior exposure. Asthmatic responses (decreased lung function measures) were found in workers who had been repeatedly exposed to formaldehyde in a number of studies (Burge *et al*, 1985; Nordman *et al.*, 1985; Hendrick and Lane, 1977). It has been proposed that this is due to allergic sensitization to formaldehyde. It is unclear what range of exposures are required to produce such sensitization. Wantke *et al.* (1996) found IgE specific to formaldehyde in children exposed in school to indoor formaldehyde. When the children were moved to a different facility with lower levels of indoor formaldehyde, the IgE levels dropped as did symptom prevalence.

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[26] H.F. Pross, *et al.*, Immunologic studies of subjects with asthma exposed to formaldehyde and urea formaldehyde foam insulation (UFFI) products. J. Allergy Clin Immunol. 79:797-810. (1987).

[27] D. Sheppard, *et al.*, Lack of bronchomotor response to up to 3 ppm formaldehyde in subjects with asthma, Envir. Res. 35:133-139 (1986).

[28] L.R. Sauder, *et al.*, Acute pulmonary response of asthmatics to 3.0 ppm formaldehyde, Toxicol. Indust. Heatlh 3: 569-578 (1987).

[29] Kulle, T.J., *et al., Acute odor and irritation response in healthy nonsmokers with formadehyde exposure,* Inhalation Tox. *5:323-332 (1993);* Kulle, T.J., *et al., Formaldehyde dose-response in healthy nonsmokers*, JAPCA 37:919-924 (1987).

[30] D.J. Green, *et al.*, Acute response to 3.0 ppm formaldehyd in exercising healthy nonsmokers and asthmatics, Am. Rev. Respir. Dis. 135:1261-1266 (1987).

Studies cited in the draft document show the presence of formaldehyde is linearly related to decreased peak expiratory flow volume in children and that the effects in asthmatic children exposed to formaldehyde at levels below 50 ppb were greater than the effects in nonasthmatic children (Krzyzanowski *et al.*, 1990). This suggests that asthmatic children are more sensitive to the pulmonary effects of formaldehyde than nonasthmatic children. In addition, as noted in the draft report, Garrett *et al.* (1999) report that low-level exposure to formaldehyde may increase the risk of allergic sensitization to aeroallergens in children. These authors also note increased respiratory symptoms in children with increasing exposure to formaldehyde in the home.

COMMENT 6: Developmental toxicity. FETEG agrees with the conclusion that formaldehyde is not a developmental toxicant, as found in the studies cited by OEHHA. For additional support, FETEG attaches a paper by Collins *et al.*, which concluded that "under exposure conditions relevant to humans, inhalation of the vapor or topical application, there is no evidence of reproductive or developmental toxicity in animal models."[31]

RESPONSE 6: OEHHA thanks the commenter for the review paper.

[31] Collins *et al.*, *A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies* (attached as Exhibit D) (manuscript submitted to and undergoing review with the Journal of Reproductive Toxicology and Epidemiology).

COMMENT 7: Potential for differential effects. OEHHA cites five studies to support its suggestion that children could be more affected than adults by formaldehyde exposure. however, there are many questions concerning the validity of these studies, and FETEG urges OEHHA to reconsider the use of these studies as support for its prioritization of formaldehyde as a contaminant that disproportionately affects children. Four of the studies used (Franklin *et al.* (2000), Garret *et al.* (1999), Wantke *et al.* (1996) and Dueva & Mizernitsky (1995)) do not contain data on adults. Therefore, a comparison of the results for children cannot be made with results for adults and a scientifically sound determination as to relative sensitivity (i.e., Children vs. Adults) cannot be made. In addition, the five studies in this section of the public review draft often contradict each other. For example, in some studies there is an effect on pulmonary function and in others there is no effect at similar formaldehyde levels. In some studies, symptoms correlate with formaldehyde concentrations and in others they do not correlate even though the formaldehyde levels are approximately the same.

RESPONSE 7: The studies cited in the report, as almost any study in the literature, do have weaknesses. However, the law requires us to list TACs that "may cause children to be especially susceptible to illness". The data in these studies do indicate that children may be at higher risk of respiratory symptoms from formaldehyde exposure. In one study, Krzyzanowski *et al.* (1990), children appeared to be more impacted than adults in terms of decrements in peak expiratory flow rate in response to formaldehyde levels in the home.

COMMENT 8: The Public Review Draft does not consider a major new report prepared by the National Academy of Sciences Institute of Medicine (IOM) that bears directly on the issues raised by the other studies in the Public Review Draft and does not support the conclusions regarding asthma. This report, entitled "Clearing the Air: Asthma and Indoor Air Exposures," was prepared by 12 experts in the field and was chaired by Professor Johnston, M.D., Department of Pediatrics, University of Colorado School of Medicine. It examined the evidence regarding the association between indoor biologic and chemical

exposures and development of asthma. The Committee discussed asthma among the general population and in sensitive subpopulations including children, and concluded that only one agent, house dust mite allergen, had "Sufficient Evidence of a Causal Relationship." In the next category, the only agent found to have a "Sufficient Evidence of an Association" was Environmental Tobacco Smoke in preschool-aged children.

The Committee also reviewed evidence regarding the association between indoor biologic and chemical exposures and the exacerbation of asthma in sensitive individuals. In this case, the agents in the category "Sufficient Evidence of a Causal Relationship" were found to be environmental tobacco smoke in preschool-aged children, house dust mite allergen, cockroach allergen, and cat allergens. Agents in the next category of "Sufficient Evidence of an Association" were found to be nitrogen dioxide; NO_x (high-level exposures at concentrations that may occur only when gas appliances are used in poorly ventilated kitchens); rhinovirus; dog allergens; and fungi/mold allergens. The Committee also found that a variety of strategies, such as removing a pet, intensive cleaning, prohibiting smoking and controlling indoor humidity might help alleviate asthma symptoms.

Further, according to the IOM report, several of the five studies relied upon by OEHHA fail to identify causative agents with substantial evidence in children and/or have not controlled for variables, such as humidity/dampness, identified as important confounding factors in the IOM report.

RESPONSE 8: As noted in our response to comment 7 above, the law does not require us to prove beyond a doubt that a chemical causes illness in children. Rather we need to list TACs that "may cause children to be especially susceptible to illness". The fact that there are confounders in the studies cited is neither unusual for epidemiology studies nor fatal in our opinion. The studies all indicate respiratory symptoms, including decreases in lung function, that correlate with formaldehyde levels in the indoor environment of the children studied.

COMMENT 9: As for the specific studies cited by OEHHA, the Franklin *et al.*[32] study from Australia measured exhaled nitric oxide as an indicator of subclinical inflammatory response in 224 children. The authors report increased nitric oxide in the breath of children in homes with over 50 ppb versus under 50 ppb formaldehyde. The range and mean exposure values are not provided. There were no measurements of the outdoors or school exposures to these children. The nitric oxide results were independent of atopy, and thus their significance is unclear. The study showed formaldehyde concentrations in the home had no effect on FVC or FEV_1 measures of pulmonary function in the children. The study does not compare children and adults, since relevant data for adults were not collected.

RESPONSE 9: As noted in the report, Franklin *et al* (2000) report significantly elevated NO levels in the breath of children living in homes with formaldehyde concentrations above 50 ppb relative to those children living in homes with formaldehyde concentrations less than 50 ppb. The children studied had no current or history of upper or lower airway disease. The authors conclude that the data suggest airway inflammation associated with exposure to formaldehyde in the home. As noted by the comment, the study did not look at adults and so cannot be the basis for a comparison between children and adults. However, it is an interesting study in that it fairly clearly indicates lower airway inflammation at relatively low exposures in children. Although there were no measurements of exposure outdoors or in school of these children, it is highly unlikely that exposures outside of the home environment would be so different in the two groups as to impact the significance of the result. Franklin *et al.* (2000) also note that the differences were significant after controlling for other variables in the home environment, age, and atopic status of the children.

[32] P. Franklin *et al.*, *Raised Exhaled Nitric Oxide in Healthy Children is Associated with Domestic Formaldehyde Levels*, 161(5) Am. J. Respir. Crit. Care Med. 1759-59 (May 2000).

COMMENT 10: The draft document relies heavily on a finding by Krzyzanowski *et al.*[33] of a greater prevalence of asthma and chronic bronchitis in children whose houses had 60-120 ppb of formaldehyde. Researchers questioned a group of 298 children (ages 6 to 15) and 613 adults using a self-administered respiratory questionnaire. Using regression analysis, the investigators found no significant association between exposures in children and self-reported chronic respiratory symptoms.

Prevalence rates of chronic bronchitis or asthma reportedly diagnosed by a physician were significantly higher when residential concentrations of formaldehyde exceeded 60 ppb, especially in the presence of tobacco smoke. However, both the Public Review Draft and the study itself fail to point out an obvious difficulty from the data displayed in Tables 3 and 4 of the study. There was no dose-response relationship with formaldehyde:

Prevalence Per 100 Subjects
Reported by Krzyzanowki in Tables 3 and 4

	≤ 40 ppb	**40-60**	**>60**
Chronic Bronchitis			
No Environmental Tobacco Smoke (ETS)	4.3 (n=141)	0 (n=12)	10.0 (n=10)
ETS	1.9 (n=106)	0 (n=10)	45.5 (n=11)
Asthma			
No ETS	8.5 (n=142)	8.3 (n=12)	0 (n=10)
ETS	15.1 (n=106)	0 (n=12)	45.5 (n=11)

More than 83 percent of the subjects in the study lived in homes in which the two-week average formaldehyde concentrations were less than 4 ppb. The average

[33] M. Krzyzanowski *et al.*, *Chronic Respiratory Effects of Indoor Formaldehyde Exposure*, 52(2) Environ. Res. 117-25 (Aug. 1990).

concentration measured was 26 ppb, with only a few homes exceeding 9 ppb. Thus, average concentrations appear to be driven by a few outliers. Findings of this study are questionable in view of these levels of formaldehyde found in the home environment. In addition, there were no measurements of allergens, or other agents present in the home.

The authors did report greater changes in peak expiratory flow rate in children than in adults. The use of peak expiratory flow rates does not confirm the presence or absence of asthma or bronchitis. This finding is the only data in any of the studies cited in the Public Review Draft document to suggest differential effects in children versus adults -- hardly a convincing basis for concluding that children are more sensitive to formaldehyde. In sum, it appears that this study is at odds with the weight of the literature, and should not be relied upon absent some further verification.

RESPONSE 10: Krzyzanowski *et al* (1990) evaluated prevalence of chronic respiratory symptoms and ventilatory function in 298 children and 613 adults living in the Tucson area. Formaldehyde concentrations were measured in the home for 2 weeks. Evaluation of the effects of formaldehyde on respiratory symptoms and peak expiratory flow rates (PEFR) was conducted controlling for chronic and acute respiratory diseases, active and passive tobacco smoking, socioeconomic status, and indoor nitrogen dioxide concentrations. Respiratory symptoms were evaluated by health questionnaires which included questions on chronic respiratory symptoms. Peak expiratory flow rates (PEFR) were measured 4 times per day.

The comment indicates that over 83% of the study subjects lived in homes with less than 4 ppb formaldehyde, with only a few homes exceeding 9 ppb. The paper reports that 83% of the subjects lived in homes with formaldehyde levels less than 40 ppb with only a few homes exceeding 90 ppb. Therefore, the comment that the average exposure of 26 ppb formaldehyde "appears to be driven by a few outliers" is incorrect.

Krzyzanowski *et al.* report that overall the self-reported prevalence rates of chronic respiratory symptoms were not related to formaldehyde (broken down by exposures below 40 ppb, 41-60 ppb, and over 60 ppb). However, the study reports that asthma and bronchitis in children 15 years or younger diagnosed by physicians were more prevalent

in houses with higher formaldehyde levels. The prevalence rates of chronic bronchitis and asthma were related to formaldehyde levels measured in various locations in the homes, but as noted in the draft document, only in those exposed also to ETS. In adults, none of the respiratory symptoms or diseases were significantly related to formaldehyde levels, although the prevalence rates of chronic cough and wheeze were higher in those living in houses with more formaldehyde. The authors report that the relationship of chronic cough to formaldehyde levels was clear only in nonsmokers, and that there was significant interaction between formaldehyde levels and smoking and chronic cough in their loglinear models.

The comment states that the data do not show a dose-response for prevalence rates of respiratory disease diagnosed by a doctor and levels of formaldehyde in the home. OEHHA agrees that the data are variable, but numbers of subjects with higher exposures of formaldehyde were small. Most of the subjects were in homes with less than 40 ppb (141 with no ETS exposure and 106 with ETS exposure). Only 12 of the children were in no-ETS homes and 10 in ETS-homes with formaldehyde levels between 41 and 60 ppb, and only 10 children were in no-ETS homes and 11 in ETS-homes with formaldehyde levels greater than 60 ppb. The sample size in the latter categories creates a problem in readily observing a dose-response relationship. The comment selected only the data with small sample size from Tables 3 and 4. Nevertheless, the authors of the paper report a significant ($p<0.05$) test for trend for doctor-diagnosed asthma in children and formaldehyde concentration in ETS homes, and a significant ($p<0.001$) trend test for doctor-diagnosed chronic bronchitis and formaldehyde concentration in ETS-homes. The trend tests for combining ETS and non-ETS children were as significant or more so, both in the case of asthma ($p<0.03$) and chronic bronchitis ($p<0.001$).

Krzyzanowski *et al.* (1990), as noted in the comment and in our document, report a decrease in PEFR as formaldehyde increases, especially in children. In addition, children with asthma had greater decreases in PEFR as formaldehyde increased than did children without asthma. Furthermore, in adults the effect was apparent but small relative to the decrease in PEFR seen in children. Decrements in PEFR in adults were transient, limited to measurements made in the morning (and not other times in the day), and seen mainly

in smokers exposed to higher levels of formaldehyde. This indicates that children may be more sensitive than adults to the impacts of low-level formaldehyde on pulmonary function.

OEHHA disagrees that this study is at odds with the rest of the literature. There are a number of studies cited in the draft report showing decreased pulmonary function in response to formaldehyde exposure. There are also studies reporting increased prevalence of respiratory symptoms correlating with increased exposure to formaldehyde in the home or school environment. Taken as a whole, we believe that the studies cited in the report support listing formaldehyde as a TAC that may cause infants and children to be especially susceptible to illness.

COMMENT 11: The Dueva and Mizernitsky study[34] cited in the Public Review Draft was published in Russian and we have therefore been unable to review the study. The finding noted in California's draft document, however, relates to a combination of "industrial allergens" and apparently is not specific to formaldehyde.

RESPONSE 11: We agree that this study did not focus solely on formaldehyde. Dueva and Mizernitsky (1995) looked at rates of atopic bronchial asthma in 41 children ages 3-14 years and examined the correlation between those rates and prevalence of industry and roadways in the neighborhood. They evaluated the children for the presence of antihapten antibodies to chromium, nickel, formaldehyde, manganese and beryllium. The investigators conclude that some children were sensitized by these industrial pollutants and speculate that exposure to these pollutants in the environment predisposes children to the development of allergic airway disease. OEHHA is not relying heavily on this particular study.

[34] L.A. Dueva and I.L. Mizernikskii, [Sensitization to Industrial Chemical Allergens in Bronchial Asthmas in Children in Environmental Pollution], 2 Med. Tr. Prom. Ekol. 41-45 (1997).

COMMENT 12: Wantke *et al.*[35] studied 62 students in Austria and reported finding IgE specific to formaldehyde. However, among the 24 of the 62 children who had elevated IgE specific to formaldehyde, only 3 had RAST scores over 2.0. There was no dose-response relationship between formaldehyde levels and RAST scores. The three classrooms studied had 43, 69 and 75 ppb of formaldehyde measured, respectively. RAST scores were not elevated at 69 ppb compared to the 43 ppb classroom, as shown below.

Number of Students with
Specific IgE to Formaldehyde in Wantke, Table 2

	75 ppb (n=22)	69 ppb (n=22)	43 ppb (n=18)
RAST over 2.0	2	0	1
RAST 1.3-1.9	10	6	5
RAST 1.0-1.2	10	16	12

Thus, there does not appear to be dose-response relationship between formaldehyde and IgE. Moreover, the IgE levels in the study did not correlate with either number or severity of reported symptoms. The authors acknowledge that "IgE-mediated sensitization to formaldehyde is rare and a matter of controversy." They further state: "Our data as well as the literature [ref. omitted] do not conclusively explain the clinical relevance of specific IgE against formaldehyde." The Wantke *et al.* study did not compare children and adults, and thus also does not speak to any differential sensitivity.

RESPONSE 12: Wantke *et al.* (1996) evaluated formaldehyde-specific IgE levels in 62 schoolchildren who were attending pre-school in a building paneled with particle-board. In addition, the parents of the children filled out a health questionnaire asking about symptoms of nosebleed, rhinitis, cough and headache, and including questions about whether smokers lived in the household. Specific IgE to formaldehyde reaching RAST-classes ≥ 2 were scored as positive, while RAST scores between 1.3 and 1.9 were scored as elevated. All control children (19 non-atopic 7-10 year olds not attending the school)

[35] F. Wantke *et al.*, *Exposure to Gaseous Formaldehyde induces IgE-Mediated Sensitization to Formaldehyde in School-Children*, 26(3) Clin. Exp. Allergy 276-80 (Mar. 1996).

had RAST scores below 1.3. Elevated RAST scores were found in 24 of the 62 children attending school in the particle board-paneled classrooms. In 21 of these 24 children, the authors considered their RAST scores elevated and in the remaining 3 children the RAST scores were considered by the authors to be "pathological" (RAST ≥ 2). Twenty of the children with elevated RAST scores were re-evaluated after being moved into a classroom with lower formaldehyde levels. The mean RAST scores dropped from 1.7 ± 0.5 to 1.2 ± 0.2 ($p<0.002$).

Complaints of health symptoms correlated with formaldehyde levels in the classroom but, as noted in the comment, elevated IgE for formaldehyde did not correlate with the number or severity of symptoms. The authors note that 55% of the children in the highest-formaldehyde classroom (75 ppb) had formaldehyde-specific IgE, while 33% of the children in the lowest formaldehyde classroom (43 ppb) had formaldehyde-specific IgE. The comment states that there was no dose-response evident in formaldehyde-specific IgE. Since individual propensity for sensitization to any agent varies tremendously, lack of a clear dose-response in this study is neither surprising nor is it grounds to discount the results of the study. Symptom complaints decreased after moving the children to classrooms with lower formaldehyde levels. Objective findings of rhinitis, cough, and nosebleed decreased significantly in the children ($p<0.01$) as did subjective symptoms such as headache and dry nose. This finding suggests that formaldehyde may have been a causative agent of some of the measured symptoms, although bias and confounding of course can exist. It should be noted that the children did not test positive to cat, house dust mite, or mould sensitization. The authors conclude that chronic exposure to formaldehyde in these children induced IgE mediated sensitization.

COMMENT 13: Finally, the Public Review Draft cites Garrett *et al.*,[36] a study of asthmatic and non-asthmatic children in two small towns in Victoria, Australia. This

[36] M.H. Garrett *et al.*, *Increased Risk of Allergy in Children Due to Formaldehyde Exposure in Homes*, 54(4) Allergy 330-37 (Apr. 1999).

paper does not address differences in adult and children's responses, since relevant data for adults were not collected. It does characterize the Wantke *et al.* (1996) study relevance as "unclear" because the sensitization was not associated with symptoms. Several factors compel caution in relying on this study:

- The paper likely was based on a graduate student thesis (the acknowledgements note a postgraduate publication award), and the paper presents *extensive* multi-variate analysis. Of all the analyses performed, the study notes:

    1) a crude odds ratio for atopy of about 1.4 with an increase in bedroom levels of formaldehyde of 10 ug/m^3 (adjusted for parental asthma and sex); however, the confidence interval for this finding is 0.99 - 2.00; and
    2) an adjusted odds ratio of 1.42 for atopy with an increase in the highest recorded formaldehyde level by 20 ug/m^3 (confidence interval 0.99-2.04).

    As the majority or scientists and researchers recognize, odds ratios of 1.4 are generally not considered to be strong evidence of a causal connection.

- The study took place in two small towns "surrounded by open-cut brown coal mines and power stations, which provide considerable employment." The authors had difficulty locating nonasthmatic children to participate in the study. Outdoor measurements were taken but not reported.

- The authors note there was no significant association between formaldehyde levels and house age. This is surprising, since any offgassing of formaldehyde from wood products or other formaldehyde-containing materials would be expected to decline over time. Thus, the accuracy of formaldehyde measurements could be open to question.

- In discussing the implications of their findings, Garrett *et al.* note the increased prevalence of allergic diseases in many Western countries, and suggest that materials emitting formaldehyde have become increasingly popular at the same time. The authors apparently do not appreciate that formaldehyde resin technologies have been improved substantially over the last two decades, and that releases of formaldehyde have been greatly reduced.

- It is difficult to rule out systematic recall or selection bias in this case-control study.

- With respect to exposure issues, no personal monitors were used, and there were no associations or trends for levels reported for the bedrooms, which are the one place in the house where some form of continuous exposure is likely to occur.

- The distribution of results claimed by the investigators hardly seems to be persuasive evidence of a systematic health risk. There was no significant increase in the adjusted risk for either asthma or respiratory symptoms with increasing formaldehyde exposure.

In sum, a careful reading of the studies cited as the basis for concluding that children are differentially sensitive to formaldehyde shows essentially no support for that proposition.

RESPONSE 13: Garrett *et al.* (1999) evaluated respiratory health of 148 children in 80 households in the Latrobe Valley, Victoria, Australia. Measurements of formaldehyde were taken in various parts of the home, including the bedroom of the children, four times over a year. A respiratory health questionnaire was completed by the parents during an interview. Family history of atopy and presence of pets was noted. The frequency of respiratory symptoms over the year was evaluated. And a respiratory symptom score for each child was calculated. Skin prick tests to common aeroallergens were performed on the children. The distributions of children in three categories of formaldehyde exposure were compared by Chi-square tests with assessment of linear trends. Logistic regression models were applied to calculate adjusted odds ratios for atopy, asthma, and respiratory symptom score with formaldehyde exposure. The mean for several of the health outcome measures was compared across the three exposure categories by analysis of variance with Bonferroni correction for multiple comparisons. The comment implying that the paper is less worthwhile because it uses multiple comparisons is mitigated by use of appropriate statistical corrections such as the Bonferroni correction.

Marginally higher mean formaldehyde levels were recorded in the bedrooms of atopic children compared to nonatopic children ($p=0.06$). A significant difference in the highest measures of formaldehyde in the homes of atopic versus nonatopic children was seen ($p<0.002$). When the prevalence of atopic versus nonatopic children was evaluated based on formaldehyde levels in the bedroom and highest in the house, the linear trend test was

marginal for the bedroom concentrations ($p=0.06$) but significant for highest measurement in the house ($p<0.001$). The association between atopy in the children and formaldehyde levels in the home was not confounded by parental atopy. As noted in the comment, the odds ratio for atopy with an increase in bedroom formaldehyde level of 10 $\mu g/m^3$ was 1.4 (95% CI, 0.98-2.00). An adjusted odds ratio of 1.42 (95% CI 0.99-2.04) for atopy with an increase of 20 $\mu g/m^3$ formaldehyde in the highest recorded level for the home was observed. The comment states that an odds ratio of 1.4 is not generally considered to be strong evidence of a causal connection. While in epidemiological terms, this is a "weak" association, it is not evidence of no association. Indeed, odds ratios in this range have been used in conjunction with other evidence of causal inference as the basis for public health interventions to prevent disease (e.g., reduction in ETS exposure based on an OR of 1.2 to 1.9 for lung cancer in nonsmokers) Most odds ratios for heart disease associated with cigarette smoking are below 2, "weak" in epidemiological terms, but certainly strong in public health impacts. Thus, this criticism is not particularly useful.

In contrast to the assertion in the comment, Garrett *et al* (1999) also report a significant association ($p=0.03$) between mean respiratory symptom score and formaldehyde levels in the home (based on the highest recorded level for the home). A multiple linear-regression model was used to adjust for the effects of parental allergy or asthma and for any interaction between parental allergy, parental asthma, and formaldehyde exposure group; the association between highest formaldehyde level in the home and respiratory symptoms remained.

The comment that the publication is probably based on a graduate student's thesis also carries no weight. The paper appeared in the journal Allergy and the study had four coauthors at the University, including the Deputy Head of the Department of Epidemiology and Preventive Medicine. We note that the Garrett et al. article refers to four other articles concerning different aspects of the same set of houses. This all suggests a very thorough approach to their analysis.

The comment points out the formaldehyde levels in the home did not correlate with the age of the house. While this is interesting, it is not in itself reason to disregard the study. Actually, the previous sentence in the paper points out the reason for this lack of correlation: "Glued wood products, such as particle board and fibreboard, were the main sources of indoor formaldehyde." Many sources of formaldehyde are brought into the home (e.g., furnishings) which would influence the measurements independent of the age of the home.

The comment states that it is difficult to rule out selection bias. OEHHA agrees with this comment, and indeed the authors of the study discuss this issue. In particular the authors note that in this study because the families were volunteers, families with allergic problems may have been more likely to participate. As noted by the authors, the percent of nonasthmatic children who were atopic was somewhat higher than in other comparable community studies. However, the authors do not think this significantly influenced their results.

In discussing the fact that stronger associations were noted between highest measurement in the house and atopy or respiratory symptoms than between measurements in the child's bedroom and these measures, the investigators note that peak exposures may be most important for sensitization.

OEHHA disagrees with the comment that "a careful reading of the studies cited as the basis for concluding that children are differentially sensitive to formaldehyde shows essentially no support for that proposition". As noted in the other responses above, these studies provide evidence that formaldehyde can sensitize people at low concentrations and one study indicates that children are more sensitive than adults. In addition, respiratory symptoms are associated with formaldehyde levels in these studies. In our opinion, these studies provide sufficient justification to list formaldehyde as a TAC "that may cause infants and children to be especially sensitive to illness".

COMMENT 14: Indoor air levels. In the public review draft for formaldehyde, OEHHA describes the emissions of formaldehyde from common household products as "very high."[37]. This characterization is inaccurate given product improvements, virtual elimination of urea-formaldehyde foam insulation in homes, and advances in process technology and chemistry during the late 1980s and 1990s. Further, ambient residential measurements can vary for a myriad of reasons: sampling protocol, age of home and furnishings, location of collection points, product loading, ventilation, life-style factors, sensitivity of testing, and many others. These variables are difficult if not impossible to quantify and evaluate without in-depth study of the work that was done.

Geomet Technologies, Inc. conducted one of the most intensive and scientifically rigorous investigations in the mid-1990s, under contract with U.S. EPA.[38] The study indicated levels were well below 0.1 ppm even with high product loadings of new materials.

The EPA Home Study is noteworthy for many reasons. First, it represents perhaps the best-controlled scientific study of its kind. A new, unoccupied conventional home was obtained and loaded with different combinations of formaldehyde-emitting building products and finished materials. Readings were taken with medium and high loading scenarios. The materials used (underlayment, paneling, doors, cabinets, and countertops) were typical goods sold in the marketplace and were thoroughly characterized in chamber tests prior to installation. Researchers adopted and implemented an elaborate Quality Assurance Plan, which covered all aspects of the study including variables such as air leakage, ventilation rate, product loading and characterization, baseline testing before installation of the emitting products, sampling

[37] OEHHA, Public Review Draft, at 3.

[38] Koontz, M., H.E. Rector, D.R. Cade, C.R. Wilkes, L.L. Niang, *Residential Indoor Air Formaldehyde Testing Program: Pilot Study* (prepared for U.S. EPA, Office of Pollution Prevention and Toxics) (Mar. 21, 1996). See also an article that was jointly authored by Geomet, industry, and EPA scientists, that discusses the EPA Home Study. Hare, D., R.L. Margosian, W.J. Groah, S.W. Abel, L.G. Schweer, M.D. Koontz, *Evaluating the Contribution of UF-Bonded Building Materials to Indoor Formaldehyde Levels in a Newly Constructed Home* (Apr. 17, 1996). These studies are all attached as Exhibit E.

location and frequency, testing methodology, and sensitivity. The resulting data are highly reliable.

The EPA Study is also notable and highly credible because of how it was conducted. Geomet, an independent EPA contractor, conducted the work under the supervision of EPA scientists. An industry/EPA advisory committee provided preliminary input on the study parameters and design. The numerous factors that could impact the results were well-documented, characterized, and controlled.

It is well recognized that new materials have the highest emissions of formaldehyde. There is a "decay" phenomenon over time in which the available formaldehyde is dissipated. All things being equal, one would therefore expect the highest formaldehyde concentrations to be found in new homes. The conclusion of the study was reassuring:

> Results of the . . . study show that initial formaldehyde concentrations in the house, even at a "High" loading of UF-bonded building materials, were below 0.076 parts per million and were as much as 50 percent below the levels that had been predicted by commonly used indoor air models. After 30 days, average indoor formaldehyde concentrations in the house were less than 0.045 parts per million.

OEHHA should reference this important work in its Public Review Draft for Formaldehyde, and refrain from characterizing formaldehyde levels as "very high."

RESPONSE 14: The purpose of the formaldehyde draft summary is not to discuss all possible information on indoor levels of formaldehyde. Formaldehyde has been measured routinely in indoor air for decades. The database indicates the presence of formaldehyde in indoor air under a variety of conditions. We appreciate that the industry is making progress in reducing indoor sources of formaldehyde.

COMMENT 15: Conclusion. For the above stated reasons, FETEG urges OEHHA to revise the public review draft to more accurately set forth the current state of science concerning formaldehyde's carcinogenic properties, potential effects on asthma and pulmonary function, and the lack of evidence for a differential effect of formaldehyde on children. In light of the state of the evidence, formaldehyde should not be designated as a priority substance for children's health.

RESPONSE 15: OEHHA believes our document reflects the current state-of-the-science. We have utilized in the prioritization the cancer unit risk factor and chronic Reference Exposure Levels that have undergone public review and review by the state's Scientific Review Panel on Toxic Air Contaminants. In our opinion, formaldehyde is an important TAC and likely has greater impacts on infants and children than adults. As such we are maintaining our proposal to place it on the list of TACS "that may cause infants and children to be especially susceptible to illness," pursuant to Health and Safety Code Section 39669.5.